THE AUTHORS REPLY

We thank Drs. Tarone and McLaughlin (1) for their comments on our interpretation of the nasopharyngeal cancer findings in our study (2). Tarone and McLaughlin question the evidence for a possible association between formaldehyde exposure and nasopharyngeal cancer. We believe that the arguments they present are incorrect, because they inappropriately single out, a posteriori, one plant out of 10; compare all exposed workers with the general population and ignore exposure-response trends based on internal comparisons; compare exposure estimates across studies without consideration of differing exposure assessment methods; and emphasize duration of exposure while ignoring metrics that include intensity of formaldehyde exposure.

With a rare outcome, such as nasopharyngeal cancer, it is not surprising to find an uneven distribution of events across plants. The purpose of a multifacility study is to assemble a large enough population to evaluate risks in the aggregate. The focus on an individual plant negates the value of a multiplant study. To identify risk, it is critical to contrast the most highly exposed workers with low-exposed or nonexposed workers. Focusing on ever/never exposure comparisons, as Tarone and McLaughlin (1) have done, can hide associations, especially since only a small portion of workers is generally exposed to high levels.

We believe that internal comparisons, as we made in our paper (2), are more informative than comparisons with external rates, where the healthy worker bias is an established problem. However, even if we allow for an external comparison group, standardized mortality ratios for plant 1 alone and for plants 2–10 were elevated at the highest level for all exposure metrics (table 1). In addition, homogeneity of standardized mortality ratios for plant 1 versus plants 2–10 was not rejected for average intensity, cumulative exposure, and duration of exposure, although it was rejected for peak exposure. Given the small numbers involved, there was no clear pattern of risk heterogeneity between plant 1 and plants 2–10.

Tarone and McLaughlin's (1) conclusion that a substantially larger proportion of workers in the British cohort (3) was exposed to higher intensities of formaldehyde than in the National Cancer Institute (NCI) cohort may not be correct. The exposure assessment for the British cohort assigned the same exposure category to jobs for all time periods, whereas the NCI exposure assessment incorporated changes in exposure levels over time. Exposure levels have been decreasing over time in most factories, which complicates comparisons between these two exposure assessment approaches. Furthermore, workers in the British cohort were characterized by exposure intensity in the highest-exposure job ever held, while the metric of average intensity used in the NCI cohort represents average intensity across all exposed jobs held. These differences are likely to create the appearance of higher average levels in the British cohort.

While three of the six deaths from nasopharyngeal cancer in the NCI cohort contributed by plant 1 involved exposure for less than 1 year, three subjects had cumulative exposure

TABLE 1. Observed numbers of deaths from nasopharyngeal cancer and standardized mortality ratios among US formaldehyde workers in the highest exposure categories of four exposure metrics, by plant

Plant	Average intensity ≥1 ppm		Peak exposure ≥4 ppm		Cumulative exposure ≥5.5 ppm		Duration of exposure ≥15 years	
	Obs*	SMR*,†	Obs	SMR†	Obs	SMR†	Obs	SMR†
1	6	15.4	6	16.7	2	14.8	1	18.8
2–10	1	2.5	2	2.5	2	4.2	1	2.1
1–10	7	8.8	8	6.8	4	6.5	2	3.7
p value‡		0.114		0.025		0.426		0.379

* Obs, observed number of deaths; SMR, standardized mortality ratio.

† SMRs among nonexposed workers in plant 1, plants 2–10, and plants 1–10 were 0.0 (no deaths observed), 1.9 (two deaths observed), and 1.6 (two deaths observed), respectively.

‡ Exact two-sided *p* value from a test of homogeneity of SMRs for plant 1 and plants 2–10.

exceeding 1 ppm-year, and all six deceased workers had been in the highest peak exposure category of $\geq$4 ppm and had had average exposure intensities exceeding 1 ppm.

Our results (2) and those from the evaluation of nasopharyngeal cancer in plant 1 conducted by Marsh et al. (4), coupled with the absence of an association for a variety of other potential chemical exposures, suggest that the excess deaths in this cohort are linked to formaldehyde. Furthermore, of seven case-control studies (5–11), five have found an increased risk of nasopharyngeal cancer for overall occupational exposure to formaldehyde or in high exposure categories (6–11). These findings support our conclusion of a potentially causal association between exposure to formaldehyde and nasopharyngeal cancer.

References

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